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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,577	10/28/2003	Edwin Raymond Chapman	960296-99004	8039

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
06/19/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/695,577	CHAPMAN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,14 and 42-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,14 and 42-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/28/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2007 has been entered. Claims 10, 14 and 42-49 are under examination.

Rejections Withdrawn

2. The following rejections are withdrawn in view of Applicant's amendment and remarks:

a) rejection of claims 47 under 35 U.S.C. 112 second paragraph, page 2, paragraph 2 of the Final Office action.

b) rejection of claims 10-14 and 41-50 under 35 U.S.C. 112 first paragraph, pages 3-9, paragraph 4 of the Final Office action.

c) rejection of claims 10-14, 41-43 and 45-50 under 35 U.S.C. 102(b), pages 9-11, paragraph 5 of the Final Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10, 14 and 42-49 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10, 14 and 42-49 are directed to a complex of a ligand and a polypeptide wherein the polypeptide comprises an amino acid sequence selected form (i) amino acids 40-60 of SEQ ID NO:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B) binding domain), (ii) amino acids 40-60 of SEQ ID NO:9 (rat synaptotagmin II botulinum toxin serotype B (BoNT/B binding domain) and (iii) a fragment of mouse or rat synaptotagmin II homolog that corresponds to (i) or (ii) wherein the ligand is selected from BoNT/B and an antibody against said amino acid sequence and wherein the ligand binds to the polypeptide at said amino acid sequence with the proviso that where the polypeptide is full length synaptotagmin, the ligand is not a botulinum toxin.

The specification has not described the vast genus of complexes encompassed by the claims. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

The closet prior art is Kozaki et al *(Microbial Pathogenesis, 1998, 25, 91-99)* which teach complexes comprising deletion mutants which contain the N-terminal domain with the transmembrane domain (amino acids 1-87) and without the transmembrane region (amino acids 1-63) of synaptotoagmin II. Kozaki et al do not teach the a complex wherein the polypeptide comprises (i) an amino acid sequence of amino acids 40-60 of SEQ ID NO:7 or (ii) amino acids 40-60 of SEQ ID NO:9 or (ii) fragments of (i) and (ii). Thus, instant specification nor the prior art provide guidance as to the structural limitations regarding the fragments or variants that are encompassed broadly claimed genus of complexes. The specification nor the prior art provide the critical elements that are disclosed in the current claims. Thus, the skilled artisan would reasonably conclude that Applicant has not provided written description for the claimed genus of complexes.

The claims invention is directed to fragments and variants of the polypeptide used in the complex. To adequately describe the genus of complexes one must describe the structure of the complex including the structure of the polypeptide used in the complex. It should be noted that the claims recite the language "wherein the polypeptide comprises an amino acid sequence selected form (i) amino acids 40-60 of SEQ ID NO:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B) binding domain), (ii) amino acids 40-60 of SEQ ID NO:9 (rat synaptotagmin II botulinum toxin serotype B (BoNT/B binding domain) and (iii) a fragment of mouse or rat synaptotagmin II homolog that corresponds to (a) or (ii).

The instant specification has described complexes that comprise synaptotagmin II amino acids 1-267, complexes that comprise synaptotagmin II amino acids 61-267 and complexes that comprise synaptotagmin II amino acids 1-87. The instant specification does not describe fragments of the polypeptides of amino acids 40-60 of SEQ ID NO:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B) binding domain) or fragments of amino acids 40-60 of SEQ ID NO:9 (rat synaptotagmin II botulinum toxin serotype B (BoNT/B binding domain).

The instant specification has not described how one would begin to choose "fragments of amino acids 40-60 of SEQ ID NO:7 or fragments of amino acids 40-60 of SEQ ID NO:9 or variants that retain the recited function of binding to a ligand.

". The specification does not support the broad scope of the claims, which encompass fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;

- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide no written description such that one skill in the art could determine which of the essentially infinite possible choice is likely to be successful.

The claims of the instant application are drawn to complexes that are formed *in vivo* in a mammal. See claim 47 in particular. The instant specification has not described how one of skill in the art would form the claimed complex in a mammal. The specification has not provided written support for the broad scope of the claims, which encompass a vast number of complexes being formed *in vivo*. How does the skilled artisan form a complex that comprises a ligand and a polypeptide that is a fragment of amino acids 40-60 of SEQ ID NO: 7 and amino acids 40-60 of SEQ ID NO:9 BoNT/B-binding of murine synaptotagmin II *in vivo*?

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. *(Nature Biotechnology 7: 936-937, 1999)*, defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural

characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of complexes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of complexes capable of specifically binding to the claimed polypeptide of the complex. Consequently, the art is unpredictable, MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d

1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. *The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, `Written Description" Requirement (66 FR 1099-1111, January 5, 2001)* state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of complexes, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

Moreover, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of complex to which the claims are drawn, such as a correlation between the complex and reduced binding

activity between botulinum toxin B and murine synaptotagmin II so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of complexes. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of complexes on which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of complexes that provide reduced binding activity between botulinum toxin B and murine synaptotagmin II.

In view of the above, the instant specification fails to meet the written description in regards to the genus of complexes broadly claimed.

Scope of Enablement

4. Claims 10, 14 and 42-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for directed to a complex of a ligand and a polypeptide wherein the polypeptide comprises the amino acid sequence selected from (i) amino acids 40-60 of SEQ ID NO:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B) binding domain) and the amino acids 40-60 of SEQ ID NO:9 (rat synaptotagmin II botulinum toxin serotype B (BoNT/B binding domain) wherein the ligand is selected from BoNT/B and an antibody against said amino acid sequence and wherein the ligand binds to the polypeptide at said amino acid sequence with the proviso that where the polypeptide is full length synaptotagmin wherein the ligand is not a botulinum toxin., does not reasonably provide enablement for complex of a ligand

and a polypeptide wherein the polypeptide comprises the amino acid sequence that is a fragment of amino acids 40-60 of SEQ ID NO:7 or a fragment of SEQ ID NO:9 wherein the ligand is selected from BoNT/B and an antibody against said amino acid sequence and wherein the ligand binds to the polypeptide at said amino acid sequence with the proviso that where the polypeptide is full length synaptotagmin wherein the ligand is not a botulinum toxin.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and uses the invention commensurate in scope with these claims.

The instant specification teaches that P21, which is a BoNT/B binding domain consisting amino acids 40-60 of SEQ ID NO: 7 and amino acids 40-60 of SEQ ID NO:9 was used in an immunoassay and mediates binding of BoNT/B (pages 22-24). Thus, the instant specification is enabled for this embodiment.

The instant specification does not place any structure limitations on the fragments or variants of the complexes encompassed by the claims. The claims include numerous structural fragments or variants and the genus is highly variant because a significant number of structural differences between genus member is permitted. The specification and the claims do not provide any guidance on the structure of the fragments or variants encompassed by the claims nor does the specification provide any guidance as to what changes can or cannot be made without causing a detrimental effect or will result in a complex that is not encompassed by the claims or described by

the specification. The general knowledge of the art does not supplement the omitted description because specific, not general guidance is needed.

The closest prior art is Kozaki et al *(Microbial Pathogenesis, 1998, 25, 91-99)* which teaches complexes comprising deletion mutants which contain the N-terminal domain with the transmembrane domain (amino acids 1-87) and without the transmembrane region (amino acids 1-63) of synaptotoagmin II. Kozaki et al do not teach the a complex wherein the polypeptide comprises (i) an amino acid sequence of amino acids 40-60 of SEQ ID NO:7 or (ii) amino acids 40-60 of SEQ ID NO:9 or (ii) fragments of (i) and (ii). Thus, instant specification nor the prior art provide guidance as to the structural limitations regarding the fragments or variants that are encompassed broadly claimed genus of complexes. The specification nor the prior art provides the critical elements that are disclosed in the current claims. Thus, the skilled artisan would reasonably conclude that Applicant has not provided enablement for the claimed genus of complexes.

The teachings of the prior art in regards to sequence variation are cited below:

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties*, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort

the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability. Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach*, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect. *Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering,* 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Therefore, only a complex comprising a polypeptide consisting of amino acids 40-60 of SEQ ID NO: 7 and amino acids 40-60 of SEQ ID NO:9 a but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the enablement requirement under 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of

experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other complexes having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skilled in the art would require guidance, in order to make or use complexes that fragments of consisting amino acids 40-60 of SEQ ID NO: 7 and amino acids 40-60 of SEQ ID NO:9 or variants thereof in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the complex's structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd.

927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 10 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the claimed invention. Claim 10 recites "wherein the ligand is selected from "BoNT?B and an antibody against said amino acid sequence". Claim 10 also recites "the ligand is not a botulinum toxin. It is unclear as to what Applicant intends since botulinum toxin serotype B is a botulinum toxin. What does Applicant intends to constitute the ligand of the complex? Appropriate clarification and/or correction is required.

Status of Claims

6. No claims allowed.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
June 1, 2007

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER